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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,930	05/30/2006	Charles Van Hove	DECLE59.012APC	8689

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EXAMINER	
ZAREK, PAUL E	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
12/18/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/580,930	VAN HOVE ET AL.	
	Examiner	Art Unit	
	Paul Zarek	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24,29 and 30* is/are pending in the application.

4a) Of the above claim(s) *14-23,29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *0530/2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/30/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1 and 3-6 have been amended and Claims 25-28 have been cancelled by the Applicant in correspondence filed on 10/07/2008. Claims 1-24, 29, and 30 are currently pending. This is the first Office Action on the merits of the claim(s).

Election/Restrictions

2. Applicant's election with traverse of Group I, drawn a compound of formula (I), and the species of formula (I) wherein R^1 is glucopyranosyl, and R^2, R^3, and R^4 are C_{1-6} alkyl in the reply filed on 10/07/2008 is acknowledged. The traversal is on the ground(s) that the claims have been amended such that R4 can no longer be hydrogen, thus the amended claims share a special technical feature. This is not found persuasive because the requirement for restriction is based upon the claims as presented, not as amended.

The requirement is still deemed proper and is therefore made FINAL.

3. Examiner notes that Applicant did not specifically elect a single species of formula (I). Applicant did not specify the number of double bonds in the pyran ring, nor specify the exact identity of the alkyl groups (i.e. methyl, ethyl, etc.). Therefore, Examiner is interpreting that pyran rings possessing zero, one, or two double bonds are obvious variants of each other. Claims 1-13 and 24 read on the elected species. Claims 14-23, 29, and 30 are withdrawn as being drawn to a nonelected group.

Priority

4. Applicant's claim for the benefit of a prior-filed international application PCT/EP03/13406 (filed on 11/28/2003) under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. The effective filing date for the instant application is 11/28/2003.

Claim Rejections - 35 USC § 112 (1st paragraph)

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-13 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound or composition of formula (I), or salts, stereoisomeric forms, and racemic mixtures, thereof, does not reasonably provide enablement for a prodrug, esters, or metabolite of formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

7. *In re Wands*, 858 F.2d at 736-40, 8 USPQ2d at 1403-07, set forth eight factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (MPEP § 2164.01(a))

a. *The breadth of the claim*: Claim 1 of the instant application is drawn to a compound or pharmaceutical composition of formula (I) and salts, stereoisomeric forms,

racemic mixtures, prodrugs, esters, and metabolites thereof. The instant specification defines "prodrug" to be "functional derivatives . . . that are readily convertible in vivo into the required compound" (pg 9, lines 27-28). "Metabolite" is not defined in the instant specification and is therefore interpreted to include any compound that is the result of the breakdown of the formula (I). Therefore, a prodrug of formula (I) is interpreted to be a metabolite of formula (I). "Esters" are also interpreted to be prodrugs. Claims 2-13 and 24 depend upon Claim 1, and possess all the limitations therein;

b. *Nature of the invention*: The nature of the invention is a compound or composition of formula (I), or any salt, stereoisomeric forms, racemic mixtures, prodrugs, esters, and metabolites thereof.;

c. *The state of the prior art*: Prodrugs are known in the art and are utilized to improve the targeting or pharmacokinetics of a given drug. Van de Waterbeemd, et al. (Journal of Medicinal Chemistry, 2001) teach the myriad considerations one must keep in mind when designing prodrugs (pgs 1314-1327);

d. *Level of one of ordinary skill in the art*: Medicinal chemists would represent one of ordinary skill in the art. Consequently, the level of ordinary skill would be high;

e. *Level of predictability in the art*: Numerous factors must be considered when attempting to create a prodrug. Van de Waterbeemd, et al., state that even with high-throughput screening and combinatorial chemistry, "the attrition of the eventual development candidates is still very high mainly due to toxicity and/or poor [pharmacokinetic] properties" (pg 1327, "Future Directions" paragraph 1, emphasis added). It cannot be known *a priori* whether a given molecule will be an effective

prodrug. High-throughput computer modeling is not yet competent to reliably predict whether a given molecule would be an effective prodrug of a given drug. As such, "there remains a need for relatively low-throughput animal studies to extrapolate the likely clinical pharmacokinetic profile (van de Waterbeemd, et al., pg 1328, paragraph 1). Van de Waterbeemd, et al., further teach that it is unclear which mathematical models would be most suited to predict pharmacokinetic properties of a given molecule in lieu of experimental data (pg 1328, paragraph 3). Finally, van de Waterbeemd, et al., discuss that "much needs to be learned about transporters influencing either active drug uptake or efflux of orally administered drugs. In addition, it will be important to develop screens to assess its extent" (pg 1328, "Conclusions);

f. *Amount of direction provided by the inventor*: Applicant does not provide any rationale for what would be considered a prodrug or metabolite of formula (I);

g. *Existence of working examples*: There are no working examples of a prodrug or metabolite of formula (I); and,

h. *Quantity or experimentation needed to make or use the invention based on the content of the disclosure*: Predicting if a certain molecule is in fact a prodrug that produces the active compound metabolically, in humans, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests: A) it must itself be biologically inactive; B) it must be metabolized to a second substance, *in vivo*, at a rate and to an extent to produce that second substance at a physiologically meaningful concentration;

and C) the second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation. The instant specification does not provide enabling guidance sufficient that one of ordinary skill in the art would understand which of the potentially limitless candidates would be a legitimate prodrug of the compound of formula (I). The prior art does not compensate for this deficiency. Therefore, it would require undue and unpredictable experimentation to make the invention commensurate with the scope of the rejected claims.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-4, 7, 9, 11-13, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koskela, et al. (Acta Horticulture, 2001, provided in IDS).

11. Claims 1-4, 7, 9, and 11-13 of the instant application are drawn to a compound of formula (I) comprising a 3,6-dihydro-2H-pyran ring, of which the elected species possesses a glucopyranosyl group at R^1, and R^2, R^3, and R^4 are independently C_{1-6} alkyl groups. It is noted that Applicant amended the claims such that R^4 is not hydrogen. Claim 24 is drawn to the pharmaceutical composition of a compound of formula (I).

12. Koskela, et al., teach a derivative of 3,6-dihydro-2H-pyran ring wherein R^1 is glucopyranosyl, R^2 and R^4 are –H, and R^3 is $–CH_3$ (Fig 1). Koskela, et al., further teach a pharmaceutical composition of said compound for the treatment of leaves (Fig. 2). Koskela, et al., do not teach a compound wherein R^2 and R^4 are C_{1-6} alkyl, such as $–CH_3$, or a specific stereochemistry of the compound. However, -H and $–CH_3$ are structurally similar such that one of ordinary skill in the art would not expect the substitution of –H for $-CH_3$ would confer different properties on the resultant molecule. Also, alteration of the stereochemistry would not be expected to alter the properties of the molecule. Therefore, absent unexpected results, the compound and composition of Koskela, et al., render the elected species *prima facie* obvious.

Claims 1-3, 5, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wepple, (ACS Symposium Series, 1987, provided in IDS).

13. Claims 1-3, 5, and 7 of the instant application are drawn to a compound of formula (I) comprising a tetrahydro-2H-pyran ring, of which the elected species possesses a glucopyranosyl group at R^1, and R^2, R^3, and R^4 are independently C_{1-6} alkyl groups. It is noted that Applicant amended the claims such that R^4 is not hydrogen.

14. Wepple teaches a derivative of tetrahydro-2H-pyran ring wherein R^1 is glucopyranosyl, R^2 and R^4 and –H, and R^3 is $–CH_3$ (Compound 3). Wepple does not teach a compound wherein R^2 and R^4 are C_{1-6} alkyl, such as $–CH_3$, or a specific stereochemistry of the compound. However, -H and $–CH_3$ are structurally similar such that one of ordinary skill in the art would not expect the substitution of –H for $-CH_3$ would confer different properties on the resultant molecule. Also, alteration of the stereochemistry would not be expected to alter the properties of the molecule. Therefore, absent unexpected results, the compound of Wepple renders the elected species *prima facie* obvious.

15. Claims 1-3, 6, 7, and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gafner, et al. (Helvetica Chimica Acta, 1998, provided in IDS).

16. Claims 1-3, 6, 7, and 10-12 of the instant application are drawn to a compound of formula (I) comprising a pyran ring, of which the elected species possesses a glucopyranosyl group at R^1, and R^2, R^3, and R^4 are independently C_{1-6} alkyl groups. It is noted that Applicant amended the claims such that R^4 is not hydrogen.

17. Gafner, et al., teach a derivative of pyran ring wherein R^1 is glucopyranosyl, R^2 and R^4 and –H, and R^3 is $–CH_3$ (Compound 9). Gafner, et al., do not teach a compound wherein R^2 and R^4 are C_{1-6} alkyl, such as $–CH_3$, or a specific stereochemistry of the compound. However, -H and $–CH_3$ are structurally similar such that one of ordinary skill in the art would not expect the substitution of –H for $-CH_3$ would confer different properties on the resultant molecule. Also, alteration of the stereochemistry would not be expected to alter the properties of the molecule. Therefore, absent unexpected results, the compound of Gafner, et al., renders the elected species *prima facie* obvious.

Conclusion

18. No claims are allowed

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Zarek whose telephone number is (571) 270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/Rita J. Desai/
Primary Examiner, Art Unit 1625